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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,745	06/19/2003	Steven Baranowitz	1142/1E489US3	9743

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,745	BARANOWITZ, STEVEN	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/856,881.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *January 5, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application is a divisional application of US patent application 09/856881, filed May 24, 2001, now US patent 6670397, which is a national stage entry of international patent application PCT/US00/21015, filed July 31, 2000, which claims benefit of provisional applications 60/146272, filed July 29, 1999 and 60/168558, filed December 2, 1999. Claims 1-13 are pending in this application and examined on the merits herein.

Information Disclosure Statement

The information disclosure statement filed June 19, 2003 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it does not list the article title, journal title, or volume number of the non-patent literature references cited. Based upon the information disclosure statement as filed, it is impossible to determine which articles of non-patent literature are indicated therein. In addition, the information disclosure statement has been submitted as form PTO-892 rather than form PTO-1449 and is listed as being directed to application 09/856881 instead of the present application 10/600745. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. See 37 CFR 1.97(i).

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 recites the limitation "wherein said dedifferentiating step (a) is performed by a method selected from **repeated sticks with a needle at the site of injury or damage, surgically opening the site of injury or damage, and subjecting the site of injury or damage to a laser burn**." Claim 3 recites the limitation "wherein said dedifferentiating step (a) is **performed by physically or enzymatically separating the cells in said tissue or organ**." There is insufficient antecedent basis for these limitations in the claims. Both claims depend from claim 1, in which step (a) is limited to, "dedifferentiating the cells at the site of injury **by administering a dedifferentiating effective amount of an agent selected from retinoids, 12-O-tetradecanoylphobol-13 acetate, 0.1M hydrochloric acid (pH<5), hypertonic saline (saturated NaCl), a copper chelator selected from triethylamine tetrahydrochloride, and heavy metals selected from copper, zinc, and cadmium**. Claim 1 does not include within its scope methods in which step (a) involves either, "repeated sticks with a needle at the site of injury or damage, surgically opening the site of injury or damage, and subjecting the site of injury or damage to a laser burn," (Claim 2) or, "physically or enzymatically separating the cells in said tissue or organ." (Claim 3) Thus the limitations of claims 2-3 lack antecedent basis in the claims.

Claim 9 recites the limitation, which is included in the limitations of dependant claims 10 and 11, "wherein the agent in step (b) which causes transdifferentiation is **the same agent** which causes stabilization in step (c)." Parent claim 5 defines step (b) as including, "contacting said dedifferentiated cells of step (a) with an amount of **guanosine**," and step (c) as "contacting said cells from step (b) with an amount of **beta-carotene**." **As guanosine and beta-carotene are different compounds, a method in which the agent of step (b) is the same as the agent of step (c), as in the method of claim 9 and its dependant claims 10 and 11, is not included within the limitations of claim 5**. Thus the limitations of claims 9-11 lack antecedent basis in their parent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of regeneration the lens by dedifferentiating and transdifferentiating cells using those agents recited by the specification, does not reasonably provide enablement for methods of regenerating any tissue or organ in a mammalian subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The invention concerns a therapeutic method by which a damaged or destroyed tissue or organ in a mammalian subject is regenerated. This method comprising dedifferentiating, transdifferentiating, and stabilizing cells at the site of injury in order to produce cells of a type not normally produced during healing. The dedifferentiation step may be either physical or chemical. Physical methods of dedifferentiation include physical trauma and in some embodiments of the invention the initial traumatic injury which is being treated may serve as the dedifferentiation step.

The state of the prior art: The regeneration of mammalian tissues and organs is less well understood than that of other model systems, particularly amphibians. Unlike amphibians, mammals do not normally regenerate most tissues and organs in response to amputation. According to Muller et al. (reference included with PTO-892) "The transition from urodele limb studies to experimental attempts to induce a regenerative response in higher vertebrates has met with few successes, all of them restricted to anuran amphibians, and none resulting in a normal limb. This has led to the general

conclusion that a 'magic bullet' for regeneration is unlikely, but that the induction of a regeneration response will involve a coordinated effort to overcome multiple barriers to regeneration," and, "Thus, there are three different experimental approaches [urodele amphibian limb regeneration, mammalian fingertip regeneration, and mammalian fetal regeneration] that are relevant to the long-term goal of an enhanced regenerative response in humans." (p. 405, right column, second paragraph)

Therapeutic methods for regenerating lost or damaged organs, limbs, and other complex structures in mammals are not part of the current state of the medical art. Therapeutic methods for promoting wound healing are known and practiced, but wound healing is a process which differs in important respects from organ and tissue regeneration.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The regeneration of tissues and organs in mammals is a complex and poorly understood process, in part because it is very uncommon. Prior art concerning regeneration in amphibians cannot be considered to be adequately predictive for mammalian regeneration, in part because regeneration of complex structures such as limbs is a naturally occurring process in amphibians but not in mammals.

The Breadth of the claims: The claimed therapeutic methods concern methods for regenerating any mammalian tissue or organ. Claim 5 is interpreted as applying to any "mammalian tissues or organs," including those removed from the original host. Thus the claimed method need not be practiced on a living mammal. For example, the

claimed invention would include a method of regenerating a head in a decapitated mammal, provided that a method was developed for maintaining the biological survival of the remaining tissues and organs of said mammal while the head was being regenerated. The invention of claim 5 and its dependant claims is also interpreted as including *in vitro* methods, such as the *in vitro* production of whole organs from mammalian tissue samples. This interpretation finds support in the embodiment mentioned on p. 9, lines 1-6, in which pancreatic cells are transdifferentiated into liver cells *in vitro* to be reintroduced into a mammalian subject. Claim 1 and its dependant claims apply solely to the regeneration of tissues and organs in the body of a mammal, although said mammal could be brain dead at the time that the method is practiced. (e.g. for the production of additional organs from a transplant donor)

The amount of direction or guidance presented: The specification provides a theoretical background for the invention, suggesting that the claimed invention works through the reconstitution or creation of morphogenic fields. Additionally, a number of suggested protocols are provided whereby the invention could be practiced to regenerate specific mammalian tissues.

The presence or absence of working examples: One working example is given, in which Mongolian gerbil lenses are regenerated *in vivo*. (p. 18-22) This example demonstrates that the claimed invention is useful for the regeneration of mammalian lenses. No working examples are given for the regeneration of liver, limbs, or other tissues or organs.

Brockes (Reference included with PTO-982) states that, "Regeneration of the lens proceeds without the complex aspects of pattern formation seen in the limb and has the advantage of occurring through the transitions of a single cell type: the pigmented epithelial cell (PEC) of the iris." And also, "Although newts are the only adult vertebrates that are able to regenerate the lens, the ability of cultured PECs of the iris or retina to dedifferentiate and transdifferentiated into lens cells is quite widespread under appropriate conditions in culture, where chick and even human PECs will form lens cells and express crystallins." (p. 82, right column, second paragraph, p. 83, left column, first paragraph) Thus lens regeneration is a special case in which regeneration takes place much more readily than it does in other tissues and organs, such as whole limbs, and a working example disclosing lens regeneration cannot be taken as applying universally to the regeneration of all tissues and organs.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as regeneration of mammalian tissues and organs. See MPEP 2164.

The quantity of experimentation necessary: There exist a wide variety of embodiments of the claimed invention which have not been illustrated by working examples in the specification. These include, but are not limited to: regeneration of heart, liver, kidney, intestine, or other internal organs, regeneration of amputated limbs, regeneration of neural tissue in a subject suffering from neurodegenerative disease, regeneration of skin in a subject suffering from severs burns, regeneration of spinal cord in a subject suffering from paralysis, replacement of severely decayed teeth,

replacement of bone marrow in a subject undergoing chemotherapy or radiation therapy, and *in vitro* production of organs for transplantation. If a fertilized zygote is interpreted as being a "tissue or organ" in the language of the instant claims, the claimed invention would also cover methods of mammalian cloning involving dedifferentiation of a somatic cell into a totipotent precursor. These and other embodiments included within the scope of the instant claims span a wide variety of tissues and organs which are not expected to be equally responsive to the same therapeutic method. In the process of determining the range of embodiments for which the method of the disclosed working example is functional, a skilled practitioner of the relevant art would perform numerous *in vivo* tests in various animal models. Animal experiments include, along with induction of the disease state, administration of the therapy to be tested and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential tissues and organs which could be regenerated, these animal experiments would need to be many times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible therapeutic method falling within

the claimed invention, thus presenting an a burden of undue experimentation to one skilled in the art practicing the invention over the full range of tissues and organs.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the undefined and unpredictable nature of the art, the breadth of the claims, and the relative lack of working examples, Applicants fail to provide information sufficient to practice the claimed invention for the regeneration of any mammalian tissue or organ other than the lens.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerber et al. (Reference included with PTO-892)

Gerber et al. discloses a series of experiments concerning the usefulness of vitamin A compounds, including retinoic acid and β-carotene, for promoting wound healing. The procedure used involved surgically wounding an experimental animal and

then feeding said animal with a diet supplemented with the compound to be studied during t 5 or 14 day recovery period. (p. 1556, right column, under the heading *Surgical procedures*, p. 1557, left column, paragraphs 4-5 and right column, paragraphs 1-2, under the heading *Experimental Design*) Retinoic acid, although it inhibited wound healing at low doses, was found to improve healing when administered at an optimal dose of 5.0 μg/g, as illustrated by improved tensile strength of the wounded tissue. (p. 1561 Table 6, p. 1562 right column fourth paragraph) The disclosed procedure, which involves surgically wounding a subject and then administering retinoic acid to promote wound healing, repeats the same steps as instant claims 9-10 (i.e. surgery followed by administration of retinoic acid) The subject population for the method of Gerber et al. consists of subjects who have been wounded by the surgical opening of a tissue, thus falling within the limitations of step (a). Additionally, wound healing is a species of tissue regeneration, and thus a procedure aimed at promoting wound healing is included within the claim limitations of the instant claims 9-10 as a "method for regenerating mammalian tissues or organs" comprising the steps described in the claims.

Thus the invention of claims 9-10 is anticipated by the prior art.

Claims 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kulkarni et al. (US patent 5712256, cited in PTO-892)

Kulkarni et al. discloses that, "The inventors have found that wound healing can be greatly enhanced by the inclusion of nucleotides, such as RNA, DNA,

oligonucleotides, purine and pyrimidine bases, or any other source in a pharmaceutical preparation. (column 7, lines 35-39) Although Kulkarni et al. describes the invention as comprising nucleotides, it is stated that, "In the discussion and description of the claims the term nucleotide will be used generically to mean a source of preformed purines and/or pyrimidines in various forms including RNA as well as individual purines and/or pyrimidines as bases, nucleosides, or nucleotides." (column 3, lines 46-51) Thus the administration of guanosine for the promotion of wound healing is described by Kulkarni et al. Kulkarni et al. additionally discloses that, "Wounds may be the result of accident or surgery," (Column 1, lines 21-22) and "It is projected that it will be beneficial to place many, if not all, surgery patients on a nucleotide pre-treatment regimen to promote the more rapid healing of incisions, etc. that occur during surgery." (Column 10, lines 38-41) Thus Kulkarni et al. discloses as a subject populations subjects who have had their tissues or organs surgically opened, as described in part (a) of instant claim 5. Therefore, the disclosure of Kulkarni et al. includes a method comprising surgically opening a tissue or organ of a subject, who may be a mammal, and then administering guanosine in order to promote healing of the surgical incision. As wound healing is a species of tissue regeneration this method falls within the limits of instant claims 9 and 11.

Thus the invention of claims 9 and 11 is anticipated by the prior art.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kulkarni et al. (US patent 5712256, cited in PTO-892) in view of Gerber et al. (Reference included with PTO-892)

Kulkarni et al. discloses that, "The inventors have found that wound healing can be greatly enhanced by the inclusion of nucleotides, such as RNA, DNA, oligonucleotides, purine and pyrimidine bases, or any other source in a pharmaceutical preparation. (column 7, lines 35-39) Although Kulkarni et al. describes the invention as comprising nucleotides, it is stated that, "In the discussion and description of the claims the term nucleotide will be used generically to mean a source of preformed purines and/or pyrimidines in various forms including RNA as well as individual purines and/or pyrimidines as bases, nucleosides, or nucleotides." (column 3, lines 46-51) Thus the administration of guanosine for the promotion of wound healing is described by Kulkarni et al. Oral administration is disclosed as possible route of administration for the guanosine. (Column 8, lines 33-37) Kulkarni et al. additionally discloses that, "Wounds may be the result of accident or surgery," (Column 1, lines 21-22) and "It is projected that it will be beneficial to place many, if not all, surgery patients on a nucleotide pre-treatment regimen to promote the more rapid healing of incisions, etc. that occur during

surgery." (Column 10, lines 38-41) This disclosure is identical to steps (a) and (b) of claims 2 and 5-8, in which a mammalian tissue is surgically opened and then guanosine is administered after surgery. Kulkarni et al. does not disclose a procedure involving surgically opening a mammalian organ or tissue, followed by administration of both guanosine and β-carotene or retinoic acid.

Gerber et al. discloses a series of experiments concerning the usefulness of vitamin A compounds, including retinoic acid and β-carotene, for promoting wound healing. The procedure used involved surgically wounding an experimental animal and then feeding said animal with a diet supplemented with the compound to be studied during a 5 or 14 day recovery period. (p. 1556, right column, under the heading *Surgical procedures*, p. 1557, left column, paragraphs 4-5 and right column, paragraphs 1-2, under the heading *Experimental Design*) β-Carotene was found to noticeably promote wound healing, as illustrated by improved tensile strength of the wounded tissue. (p. 1560 Table 5, p. 1562 right column second paragraph) Retinoic acid, although it inhibited wound healing at low doses, was found to improve healing when administered at an optimal dose of 5.0 μg/g, as illustrated by improved tensile strength of the wounded tissue. (p. 1561 Table 6, p. 1562 right column fourth paragraph)

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Kulkarni et al. by additionally administering either retinoic acid or β-Carotene to the subject in order to further promote wound healing, as described in step (c) of claims 2 and 5-8.

One of ordinary skill in the art would have been motivated to modify the invention of Kulkarni et al. in this way in order to improve the recovery of a patient after surgery. One of ordinary skill in the art would have reasonably expected success in view of the fact that guanosine, retinoic acid, and β-Carotene were all known to be useful individually for promoting wound healing after surgery.

Thus the invention taken as a whole is *prima facie* obvious.

Allowable Subject Matter

Claim 12 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: Claim 12 is directed to a method of regenerating a mammalian lens after surgical opening of the eye. It is fully enabled by the specification as it bears a close resemblance to the working example given on pp. 18-22 and is limited to subject matter which has been adequately enabled by the specification. One skilled in the art would be able to practice the invention of claim 12 without performing undue experimentation. In addition, claim 12 is not seen to be taught or fairly suggested by the prior art. The closest prior art to the claimed invention are the methods of promoting wound healing in a mammal described previously as being disclosed by Gerber et al. and Kulkarni et al. The invention of claim 12 is directed to a different tissue or organ, in this case, the lens, than that of the cited references, which both concern injury of the skin. Thus the

invention of claim 12 is not seen to be anticipated by, or obvious over, the cited prior art as discussed above.

Summary

Claims 1-11 and 13 are rejected. Claim 12 is objected to but would be acceptable if rewritten in independent form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Eric Olson

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